

1,5-DIARYL-3,3-DISUBSTITUTED-1,5-PENTANEDIONE – A SYNTHON FOR 2,4,6-TRISUBSTITUTED HETEROCYCLES

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Abstract : 2,4,6-Trisubstituted heterocycles are prepared by the functionalization of *gem*-disubstituents and keto functionalities in 1,5-diaryl-3,3-dimethoxycarbonyl-1,5-pentane-dione (1) and 1,5-diaryl-3-cyano-3-ethoxycarbonyl-1,5-pentanedione (4).

Introduction :

The carbon-carbon bond formation reactions are important in designing desired molecular architecture. Doping of heteroatoms within the carbon framework constitutes the development of heterocycles. In our endeavor to prepare a new class of heterocycles, we have reported the reactivity of phenacyl bromide with active methylene compounds under different conditions¹. During our studies in this area we have prepared 1,5-diaryl-3,3-disubstituted-1,5-pentanedione from the above substrates. The 1,5-diketo and *gem*-diester / cyano ester groups have been utilized to develop a new class of spiro heterocycles.²⁻⁴ In order to explore the synthetic utility of the former further studies have been taken up which is the genesis for present communication. Literature survey indicates that decarboxylation of *gem* - diester produced monocarboxylic acid.⁵ However, direct conversion of diester to mono ester is sparsely reported.⁶ In our continued interest on the study of reactivity of 1,5-diaryl-3,3-disubstituted-1,5-pentanediones, herein we report some of our recent findings in this direction.

Results & Discussion :

When 1,5-diaryl-3,3-dimethoxycarbonyl-1,5-pentanedione (1) is subjected to decarboxylation by heating in acetic acid in the presence of HCl, 1,5-diaryl-3-carboxy-1,5-pentanedione (2) is obtained. On the other hand, treatment of 1 with NaCl in DMSO furnished 1,5-diaryl-3-methoxycarbonyl-1,5-pentanedione (3) directly. Similarly, treatment of 1,5-diaryl-3-cyano-3-ethoxycarbonyl-1,5-pentanedione (4) with NaCl in DMSO gave 1,5-diaryl-3-cyano-1,5-pentanedione (5). The compound 4 on heating in acetic acid in the presence of HCl gave 2. Esterification of 2 in methanol and HCl resulted 3 (Scheme 1 & Table 1).

The presence of a broad absorption band in the region 3350-3400 cm⁻¹ (OH), 1672-1690 (Ar-CO) and 1704-1715 (COOH) in compound 2 and an absorption band around 2245-2278 (CN) in compound 5 indicates the formation of 2 and 5. Furthermore the absence of an absorption band around 1730-1740 (CO₂R) confirms their formation. The ¹H NMR spectra of 2, 3 and 5 displayed one doublet in the region 3.42-3.85 ppm which accounts for methylene protons and one multiplet in the region 4.17- 4.34 ppm for methine protons. However, 3 showed a singlet in the region 3.60-3.62 ppm for methoxy protons (Scheme 1 & Table 2).

The 1,5-diketo functionality present in 3 and 5 is explored to incorporate N, O and S to develop six membered heterocycles. Thus, the reaction of 3 / 5 with ammonium acetate in acetic acid under refluxion resulted 2,6-diaryl-4-methoxycarbonyl-1,4-dihydropyridine (6) / 2,6-diaryl-4-cyano-1,4-dihydropyridine (7). Likewise, the reaction

of **3** / **5** with phosphorus pentoxide in dry benzene gave 2,6-diaryl-4-methoxycarbonyl-4*H*-pyran (**8**) / 2,6-diaryl-4-cyano-4*H*-pyran (**9**). Similar reaction of **3** / **5** with phosphorus pentasulfide in xylene afforded 2,6-diaryl-4-methoxycarbonyl-4*H*-thiopyran (**10**) / 2,6-diaryl-4-cyano-4*H*-thiopyran (**11**) (Scheme 2 & Table 1). Displacement of the oxygen atom in **8** / **9** on treatment with excess P₂S₅ in boiling xylene also gave **10** / **11**.

The absence of C=O absorption band around 1690 cm⁻¹ in IR spectra of **6-11** indicated their formation. Apart from this **6** and **7** showed a band at 3200-3300 cm⁻¹ for NH group. The ¹H NMR spectra of **6-11** showed two doublets in the region 5.38-6.33 ppm (C₃-H & C₅-H) and 4.12 - 4.64 ppm (C₄-H). Moreover **6**, **8** and **10** displayed a singlet in the region 3.58-3.62 ppm for methoxy protons. The structures of **6-11** were further confirmed by ¹³C NMR spectra (Scheme 2 & Table 2).

Thus the functionalization of *gem*-disubstituents and keto functionalities in **1** and **4** led to a new class of 2,4,6-trisubstituted heterocycles.

Experimental

Melting points were determined on Mel-Temp apparatus and are uncorrected. Microanalyses were performed at microanalytical laboratory, University of Pune, Pune. The IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using KBr disc and wave numbers are given in cm⁻¹. ¹H NMR spectra were run on a Bruker spectropin 300 MHz spectrometer and ¹³C NMR were recorded on a Varian VXR spectrometer operating at 75.5 MHz in CDCl₃/DMSO-d₆ with TMS as an internal standard and chemical shifts were given in δ. Purity of the compounds was checked by TLC using silica gel 'G' (BDH) and ethyl acetate-hexane as eluents. The 1,5-diaryl-3,3-dimethoxycarbonyl-1,5-pentanedione (**1**) and 1,5-diaryl-3-cyano-3-ethoxycarbonyl-1,5-pentanedione (**4**) were prepared as per the literature procedure¹.

Preparation of 1,5-diaryl-3-carboxy-1,5-pentanedione (**2**).

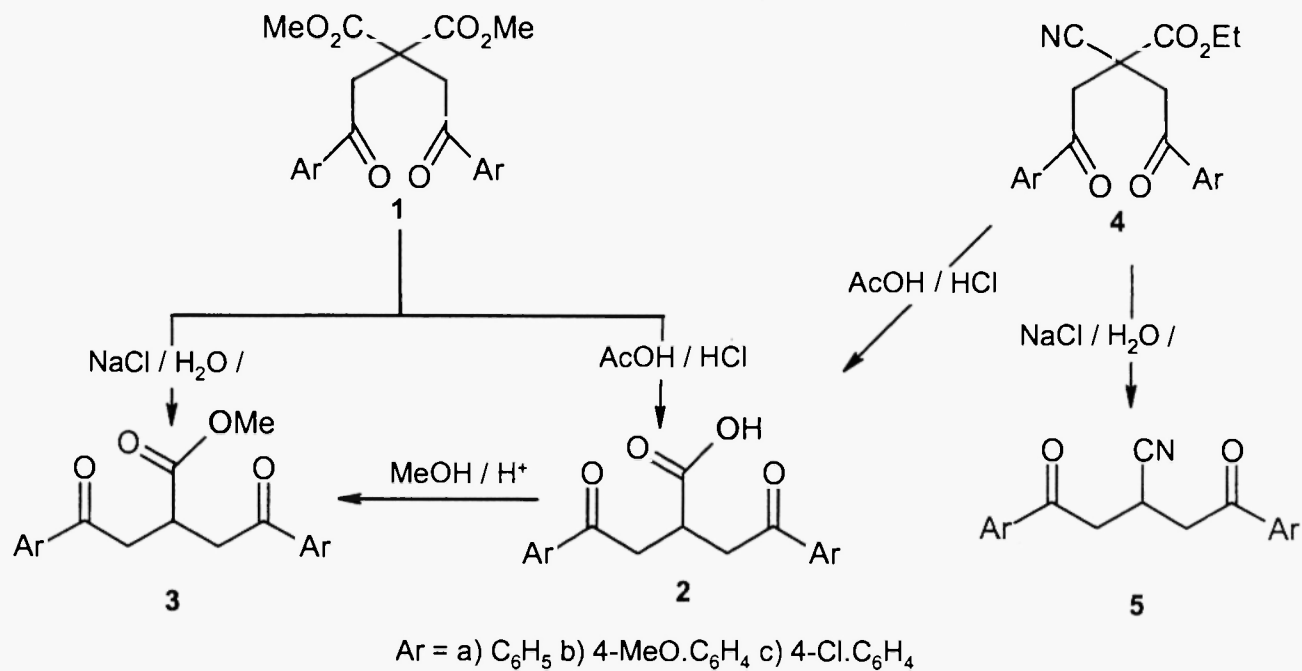
The compound **1** / **4** (0.005 mol) was heated with a mixture of AcOH (25 ml) and conc. HCl (15 ml) for 10-12 hrs. The contents were cooled and poured onto crushed ice. The thick syrupy oil was separated initially which subsequently solidified after keeping aside for a while. It was filtered, dried and recrystallized from aqueous ethanol.

Preparation of 1,5-diaryl-3-methoxy-1,5-pentanedione (**3**) / Preparation of 1,5-diaryl-3-cyano-1,5-pentanedione (**5**).

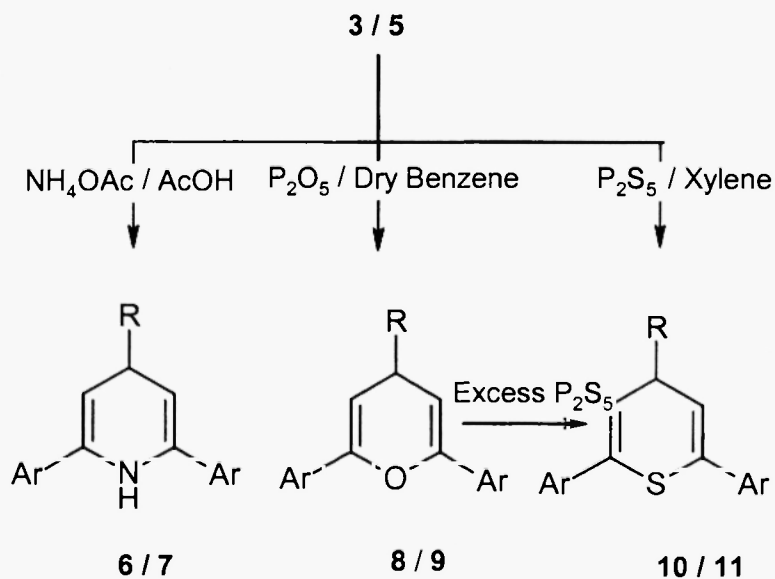
A solution of **1** / **4** (0.3 mol), NaCl (0.1 mol), water (0.6 ml) and DMSO (1 ml) was heated at 130-150 °C for 2.5 hrs. The solution was cooled and poured into water (5 ml). The solid separated was filtered, dried and recrystallized from methanol.

The compound **3** was also prepared by refluxing a mixture of **2** (0.01 mol), absolute methanol (25 ml) and concentrated sulfuric acid (1 ml) for 4-5 hrs. The contents were cooled and poured onto crushed ice. The solid separated was filtered, washed with cold water and dried. The crude product was recrystallized from methanol.

Preparation of 2,6-diaryl-4-methoxycarbonyl-1,4-dihydropyridine (**6**) or 2,6-diaryl-4-cyano-1,4-dihydropyridine (**7**).



SCHEME 1

6, 8, 10 R = CO₂Me

7, 9, 11 R = CN

Ar = a) C₆H₅ b) 4-MeO.C₆H₄ c) 4-Cl.C₆H₄

SCHEME 2

Table 1 : Physical data for compounds 2, 3 & 5-11

Compd. No.	Yield* (%)	M.P (°C)	Mol. Formula (Mol. Weight)	Found (Calcd.) %		
				C	H	N
2a	65 (62)	202-204	C ₁₈ H ₁₆ O ₄ (296.33)	72.85 (72.96)	5.39 (5.44)	-
2b	66 (61)	194-196	C ₂₀ H ₂₀ O ₄ (356.38)	67.32 (67.41)	5.72 (5.66)	-
2c	63 (64)	217-219	C ₁₈ H ₁₄ Cl ₂ O ₄ (365.22)	59.34 (59.20)	3.91 (3.86)	-
3a	69 (74)	165-167	C ₁₈ H ₁₈ O ₄ (310.35)	73.48 (73.53)	5.78 (5.85)	-
3b	66 (79)	173-174	C ₂₁ H ₂₂ O ₆ (370.41)	68.00 (68.10)	6.06 (5.99)	-
3c	68 (75)	149-150	C ₁₉ H ₁₆ Cl ₂ O ₄ (379.24)	60.04 (60.18)	4.21 (4.25)	-
5a	67	129-130	C ₁₈ H ₁₃ NO ₂ (277.33)	78.10 (77.96)	5.41 (5.45)	5.17 (5.05)
5b	68	152-154	C ₂₀ H ₁₉ NO ₄ (337.38)	71.32 (71.20)	5.73 (5.68)	4.32 (4.15)
5c	66	147-149	C ₁₈ H ₁₃ Cl ₂ NO ₂ (346.22)	62.30 (62.45)	3.74 (3.78)	3.95 (4.05)
6a	74	179-181	C ₁₉ H ₁₇ NO ₂ (291.35)	78.20 (78.33)	5.95 (5.88)	4.93 (4.81)
6b	73	194-196	C ₂₁ H ₂₁ NO ₄ (351.41)	71.90 (71.78)	6.11 (6.02)	3.92 (3.99)
6c	77	165-167	C ₁₉ H ₁₃ Cl ₂ NO ₂ (360.24)	63.25 (63.35)	4.17 (4.20)	3.96 (3.89)
7a	72	156-157	C ₁₈ H ₁₄ N ₂ (258.33)	83.80 (83.69)	5.40 (5.46)	10.98 (10.84)
7b	68	188-190	C ₂₀ H ₁₈ N ₂ O ₂ (318.38)	75.57 (75.45)	5.76 (5.70)	8.65 (8.80)
7c	70	151-152	C ₁₈ H ₁₂ Cl ₂ N ₂ (327.22)	66.00 (66.07)	3.65 (3.70)	8.50 (8.56)
8a	65	164-166	C ₁₈ H ₁₆ O ₃ (292.34)	78.19 (78.06)	5.45 (5.52)	-
8b	69	149-150	C ₂₁ H ₂₀ O ₅ (352.39)	71.66 (71.58)	5.78 (5.72)	-
8c	71	173-175	C ₁₉ H ₁₄ Cl ₂ O ₃ (361.23)	63.08 (63.18)	4.00 (3.91)	-
9a	65	168-169	C ₁₈ H ₁₃ NO (259.31)	83.50 (83.38)	5.00 (5.05)	5.55 (5.40)
9b	64	176-178	C ₂₀ H ₁₇ NO ₃ (319.36)	75.11 (75.22)	5.44 (5.37)	4.51 (4.39)
9c	68	189-191	C ₁₈ H ₁₁ Cl ₂ NO (328.20)	65.80 (65.87)	3.34 (3.38)	4.20 (4.27)
10a	71 (65)	181-183	C ₁₈ H ₁₆ O ₂ S (308.40)	74.15 (74.00)	5.29 (5.23)	-
10b	65 (62)	195-197	C ₂₁ H ₂₀ O ₄ S (368.46)	68.50 (68.46)	5.50 (5.47)	-
10c	66 (60)	209-211	C ₁₈ H ₁₄ Cl ₂ O ₂ S (377.29)	60.40 (60.49)	3.68 (3.74)	-
11a	69 (64)	202-204	C ₁₈ H ₁₃ NS (275.38)	78.60 (78.51)	4.71 (4.76)	5.00 (5.09)
11b	63 (60)	193-195	C ₂₀ H ₁₇ NO ₂ S (335.43)	71.58 (71.62)	5.22 (5.11)	4.28 (4.18)
11c	65 (61)	215-217	C ₁₈ H ₁₁ Cl ₂ NS (344.27)	62.96 (62.80)	3.26 (3.22)	4.00 (4.07)

Yields in parentheses indicates: Yield obtained from 4 to 2; from 2 to 3; from 8 to 10 and from 9 to 11

Table 2 : NMR data of compounds 2, 3 & 5-11

Compd. No.	¹ H NMR (CDCl ₃ / DMSO- <i>d</i> ₆) δ, ppm	¹³ C NMR (CDCl ₃ / DMSO- <i>d</i> ₆) δ, ppm
2a	3.49 (d, 4H, C ₂ & C ₄ -H), 4.20 (m, 1H, C ₃ -H), 7.31-7.80 (m, 0H, Ar-H).	31.26 (C ₁), 40.33 (C ₂ & C ₄), 170.88 (COOH), 198.67 (CO-CH ₂ -)
2b	3.51 (d, 4H, C ₂ & C ₄ -H), 3.73 (s, 6H, Ar-OCH ₃), 4.17 (m, 1H, C ₃ -H), 7.28-7.80 (m, 8H, Ar-H).	-
2c	3.42 (d, 4H, C ₂ & C ₄ -H), 4.24 (m, 1H, C ₃ -H), 7.30-7.80 (m, 8H, Ar-H).	-
3a	3.62 (s, 3H, OCH ₃), 3.82 (d, 4H, C ₂ & C ₄ -H), 4.15 (m, 1H, C ₃ -H), 7.28-7.77 (m, 10H, Ar-H).	32.62 (C ₃), 39.87 (C ₂ & C ₄), 53.22 (OCH ₃), 173.30 (COOMe), 196.87 (CO-CH ₂ -)
3b	3.60 (s, 3H, OCH ₃), 3.73 (s, 6H, Ar-OCH ₃), 3.85 (d, 4H, C ₂ & C ₄ -H), 4.13 (m, 1H, C ₃ -H), 7.24-7.79 (m, 8H, Ar-H).	-
3c	3.60 (s, 3H, OCH ₃), 3.78 (d, 4H, C ₂ & C ₄ -H), 4.19 (m, 1H, C ₃ -H), 7.27-7.77 (m, 8H, Ar-H).	-
5a	3.58 (d, 4H, C ₂ & C ₄ -H), 4.29 (m, 1H, C ₃ -H), 7.30-7.87 (m, 10H, Ar-H).	21.64 (C ₃), 40.33 (C ₂ & C ₄), 120.61 (CN), 197.10 (CO-CH ₂ -)
5b	3.56 (d, 4H, C ₂ & C ₄ -H), 3.71 (s, 6H, Ar-OCH ₃), 4.34 (m, 1H, C ₃ -H), 7.28-7.85 (m, 8H, Ar-H).	-
5c	3.59 (d, 4H, C ₂ & C ₄ -H), 4.32 (m, 1H, C ₃ -H), 7.27-7.85 (m, 8H, Ar-H).	-
6a	3.61 (s, 3H, OCH ₃), 4.60 (t, 1H, C ₄ -H), 5.41 (d, 2H, C ₃ & C ₅ -H), 7.19-7.76 (m, 10H, Ar-H).	42.11 (C ₄), 52.78 (OCH ₃), 109.45 (C ₃ & C ₅), 140.22 (C ₂ & C ₆).
6b	3.62 (s, 3H, OCH ₃), 3.72 (s, 6H, Ar-OCH ₃), 4.64 (t, 1H, C ₄ -H), 5.38 (d, 2H, C ₃ & C ₅ -H), 7.22-7.80 (m, 8H, Ar-H).	-
6c	3.59 (s, 3H, OCH ₃), 4.61 (t, 1H, C ₄ -H), 5.39 (d, 2H, C ₃ & C ₅ -H), 7.21-7.79 (m, 8H, Ar-H).	-
7a	4.12 (t, 1H, C ₄ -H), 5.63 (d, 2H, C ₃ & C ₅ -H), 7.22-7.75 (m, 10H, Ar-H).	39.34 (C ₄), 115.01 (CN), 110.24 (C ₃ & C ₅), 142.05 (C ₂ & C ₆).
7b	4.17 (t, 2H, C ₄ -H), 3.68 (s, 6H, Ar-OCH ₃), 5.70 (d, 2H, C ₃ & C ₅ -H), 7.22-7.75 (m, 8H, Ar-H).	-
7c	4.14 (t, 1H, C ₄ -H), 5.65 (d, 3H, C ₃ & C ₅ -H), 7.23-7.78 (m, 8H, Ar-H).	-
8a	3.60 (s, 3H, OCH ₃), 4.23 (t, 1H, C ₄ -H), 5.67 (d, 2H, C ₃ & C ₅ -H), 7.25-7.79 (m, 10H, Ar-H).	44.54 (C ₄), 53.23 (OCH ₃), 93.46 (C ₃ & C ₅), 143.08 (C ₂ & C ₆).
8b	3.58 (s, 3H, OCH ₃), 3.76 (s, 6H, Ar-OCH ₃), 4.19 (t, 1H, C ₄ -H), 5.69 (d, 2H, C ₃ & C ₅ -H), 7.24-7.80 (m, 8H, Ar-H).	-
8c	3.60 (s, 3H, OCH ₃), 4.20 (t, 1H, C ₄ -H), 5.65 (d, 2H, C ₃ & C ₅ -H), 7.23-7.79 (m, 8H, Ar-H).	-
9a	4.30 (t, 1H, C ₄ -H), 5.69 (d, 2H, C ₃ & C ₅ -H), 7.24-7.75 (m, 10H, Ar-H).	39.17 (C ₄), 113.68 (CN), 92.37 (C ₃ & C ₅), 142.87 (C ₂ & C ₆).
9b	4.22 (t, 1H, C ₄ -H), 3.69 (s, 6H, Ar-OCH ₃), 5.72 (d, 2H, C ₃ & C ₅ -H), 7.23-7.78 (m, 8H, Ar-H).	-
9c	4.25 (t, 1H, C ₄ -H), 5.70 (d, 2H, C ₃ & C ₅ -H), 7.22-7.76 (m, 8H, Ar-H).	-
10a	3.59 (s, 3H, OCH ₃), 4.31 (t, 1H, C ₄ -H), 6.32 (d, 2H, C ₃ & C ₅ -H), 7.23-7.77 (m, 10H, Ar-H).	46.68 (C ₄), 52.77 (OCH ₃), 117.20 (C ₃ & C ₅), 143.47 (C ₂ & C ₆).
10b	3.61 (s, 3H, OCH ₃), 3.72 (s, 6H, Ar-OCH ₃), 4.28 (t, 1H, C ₄ -H), 6.33 (d, 2H, C ₃ & C ₅ -H), 7.20-7.79 (m, 8H, Ar-H).	-
10c	3.58 (s, 3H, OCH ₃), 4.33 (t, 1H, C ₄ -H), 6.28 (d, 2H, C ₃ & C ₅ -H), 7.25-7.78 (m, 8H, Ar-H).	-
11a	4.43 (t, 1H, C ₄ -H), 6.20 (d, 2H, C ₃ & C ₅ -H), 7.21-7.78 (m, 10H, Ar-H).	36.98 (C ₄), 114.28 (CN), 117.76 (C ₃ & C ₅), 143.47 (C ₂ & C ₆).
11b	4.41 (t, 1H, C ₄ -H), 3.72 (s, 6H, Ar-OCH ₃), 6.12 (d, 2H, C ₃ & C ₅ -H), 7.23-7.80 (m, 8H, Ar-H).	-
11c	4.45 (t, 1H, C ₄ -H), 6.17 (d, 2H, C ₃ & C ₅ -H), 7.20-7.76 (m, 8H, Ar-H).	-

A mixture of **3** / **5** (0.01 mol) and ammonium acetate (1.5 g) in acetic acid (10 ml) was refluxed for 2 hrs. The reaction mixture was cooled and poured onto crushed ice. The product obtained was recrystallized from methanol.

Preparation of 2,6-diaryl-4-methoxycarbonyl-4H-pyran (8) or 2,6-diaryl-4-cyano-4H-pyran (9).

To a solution of **3** / **5** (0.01 mol) in dry benzene (30 ml), phosphorus pentoxide (2 g) was added and refluxed for 8-10 hrs using Dean-Stark apparatus. The reaction mixture was filtered, washed with water, brine and dried. The solvent was evaporated *in vacuo*. The resultant product was recrystallized from methanol.

Preparation of 2,6-diaryl-4-methoxycarbonyl-4H-thiopyran (10) or 2,6-diaryl-4-cyano-4H-thiopyran (11).

Compound **3** / **5** (0.01 mol) was dissolved in 25 ml of xylene and phosphorus pentasulfide (0.15 mol) was added. The reaction mixture was refluxed for 10 hrs at 130-140 °C. The cooled contents were filtered to remove excess phosphorus pentasulfide. The solvent was removed under reduced pressure. The residue was recrystallized from methanol.

10 / **11** was also prepared by heating **8** / **9** (0.005 mol) and phosphorus pentasulfide (0.01 mole) in xylene for 4 hrs. The work up procedure was followed as described above.

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